REMARKS

The 35 U.S.C. §112 Rejection

Claims 9, 11-12 and 23 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. The rejection is respectfully traversed.

Claim 9 is drawn to an adenovirus modified by introducing a ligand comprising the tripeptide Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. The claimed modified adenovirus further comprises a herpes simplex virus-thymidine kinase gene. Claim 11 is drawn to a method of using the virus of claim 9 and ganciclovir to kill tumor cells in an individual. Applicants submit that the method of administering adenovirus that carries herpes simplex virus-thymidine kinase gene to an individual followed by ganciclovir treatment is a standard treatment procedure that is currently used in a number of clinical protocols. Hence, Applicants submit that it does not require undue experimentation for one of ordinary skill in the art to practice this method of killing tumor cells using the adenovirus disclosed herein.

The Examiner continues to reject the claims based on the assertion that the art of gene therapy was unpredictable at the time the claimed invention was filed. Applicants submit that the method

of claim 11 is not "gene therapy" per se. The method of claim 11 is different and distinct from the technology of gene therapy taught in the references cited by the Examiner.

First of all, the definition and scope of gene therapy needed to be defined and clarified. "Gene therapy is a technique in which a functioning gene is inserted into a human cell to correct a genetic error or to introduce a new function to the cell." (see abstract of **Sandhu** et al.) "In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease." (First sentence of **Verma** and **Somia**). Therefore, the goal of gene therapy is to replace defective genetic materials in cells with functional genetic materials that results in restoration of normal cellular function and alleviation of disease symptoms. To achieve genetic correction through gene therapy, however, requires first solving a number of technical issues such as lack of sustained transgene expression or host immune reactions as disclosed in **Verma**, **Sandhu** et al., and **Eck** et al.

In contrast, the method of claim 11 is not gene therapy as taught in the references cited above. The purpose of the claimed cytotoxic method is to use herpes simplex virus-thymidine kinase (HSV-TK) gene and ganciclovir to kill tumor cells, not to restore

cellular function. The HSV-TK/ganciclovir method does not require replacement of defective genes. Consequently, various technical hurdles associated with gene therapy as taught in the cited references will not be problems in the claimed method. For example, in the context of gene therapy, there is a need to lower host immune responses and maintain prolonged transgene expression in order to have desirable therapeutic effects. These same issues are not problems in the HSV-TK/ganciclovir method because the target cells have to be destroyed anyway. Furthermore, adenoviral vectors carrying the HSV-TK gene are usually injected directly to the tumor mass. Therefore, the problem and difficulties of targeting the vectors to the right tissue in the context of gene therapy is not an issue here.

Applicants reiterate that the method of administering adenovirus that carries the HSV-TK gene to an individual followed by ganciclovir treatment is a standard treatment procedure that is currently used in a number of clinical protocols. **Eck** et al. teach that "adenovirus vectors have been used for gene transfer of HSV-TK. **Chen** et al. (1994) demonstrated regression of experimental gliomas following *in vivo* adenovirus-mediated gene transfer and ganciclovir treatment." (page 95, right column, second paragraph).

Although transduction of thymidine kinase gene seems to be limited to tumor cells close to the injection site, this limitation can be easily "overcome in the clinical setting by more precise stereotactic treatment planning (aided by MRI and PET studies) and by multiple tumor injections." (page 95, right column, second paragraph, last sentence). Thus, **Eck** et al. clearly teach the efficacy of using adenovirus-mediated HSV-TK gene transfer followed by ganciclovir treatment to kill tumor cells, and that one of ordinary skill in the art can readily improve and adjust the method without undue experimentation.

The inventive step of claim 11 is the use of adenovirus modified by introducing a ligand comprising the tripeptide Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob. Compared to unmodified adenovirus taught in **Eck** et al., the modified adenovirus of the present invention can infect and mediate gene transfer to a higher number of cells. Enhanced HSV-TK gene transfer would obviously lead to enhanced efficacy for the HSV-TK/ganciclovir method. Thus, Applicants submit that one of skilled in the art would find it obvious to use the modified adenovirus of the present invention to improve the method of HSV-TK/ganciclovir treatment.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation (M.P.E.P. §2164.01). As discussed above in the cited references, it is the state of the art for one of ordinary skill in the art to practice without undue experimentation a method of adenovirus-mediated HSV-TK gene transfer followed by ganciclovir treatment. In view of the state of the art and the instant disclosure of a modified adenoviral vector, Applicants submit that one of ordinary skill in the art would readily use the claimed adenovirus of the present invention to improve the method of HSV-TK/ganciclovir treatment.

The Examiner further maintains that the evidence of record has not provided guidance that correlates enhanced cellular uptake of the claimed adenoviral vector with killing of tumor cells *in vivo*. Applicants respectfully disagree.

A rigorous or an invariable exact correlation is not required (M.P.E.P §2164.02). The evidence supporting the ability of a skilled artisan to make or use the claimed invention using the application as a guide need not be conclusive, but merely convincing to the artisan; what one skilled in the art knew at the time of filing

of the application is relevant (M.P.E.P. §2164.05). Applicants submit that a person having ordinary skill in this art at the time of filing of this application was well aware of the method of killing tumor cells that involves HSV-TK gene transfer and ganciclovir treatment. It was also well known in the art that unmodified adenovirus can mediate HSV-TK gene transfer, and enhanced HSV-TK gene transfer would reasonably lead to increased tumor killing in the HSV-TK/ganciclovir method. In view of the instant disclosure that provides detailed description on enhanced gene transfer by a modified adenoviral vector, Applicants submit that it is convincing to the artisan that enhanced cellular uptake and gene transfer mediated by the claimed adenoviral vector would correlate with killing of tumor cells *in vivo*. Hence, one of skilled in the art would readily use the modified adenoviral vector of the present invention to improve both HSV-TK gene transfer and the efficacy of the HSV-TK/ganciclovir method. Accordingly, Applicants respectfully request that the rejections of claims 9 and 11 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claim 23 is a dependent claim of claim 16, which is drawn to a method of increasing the ability of an adenovirus to transduce primary tumor cells *in vitro* or *ex vivo* by introducing a

ligand comprising a tripeptide Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob of said adenovirus. The specification has described in detail such modified adenovirus mediates enhanced gene transfer *in vitro* or *ex vivo* to primary tumor cells such as ovarian cancer cells obtained from patients (page 97, line 12 to page 98, line 8, Figure 17; page 100, line 20 to page 101, line 11, Figure 19), primary tumor explants (Example 29, Figure 20) and primary explant of human SCCHN cells (Example 33, Figure 25). Hence, Applicants submit that the scope of claim 23 has a reasonable correlation to the scope of the enablement provided. Accordingly, Applicants respectfully request that the rejections of claim 23 under 35 U.S.C. §112, first paragraph, be withdrawn.

The 35 U.S.C. §102 Rejection

Claims 1-4, 9, 11-12, 16, and 22-23 were rejected under 35 U.S.C. §102(e) as being anticipated by **Wickham** et al. The rejection is respectfully traversed.

The present invention is drawn to a modified adenovirus that can mediate enhanced gene transfer to primary tumor cells and method of using the same. The claimed adenovirus is modified by introducing a ligand comprising a tripeptide Arg-Gly-Asp (RGD) into

the HI loop domain of the fiber knob, wherein the fiber knob and the fiber shaft of the fiber protein are from the same serotype. The Examiner contends that **Wickham** et al. anticipates the claimed invention because **Wickham** et al. teach 1) modification in the HI loop; 2) insertion of RGD peptide; and 3) gene transfer in tumor cells. Applicants respectfully disagree.

Wickham et al. teach two different modifications of adenovirus (see Figures 1 and 2). The first modification generates an adenovirus that has a recombinant fiber protein consists of an Ad5 fiber shaft and an Ad2 fiber knob (Figure 1), i.e. the fiber shaft and the fiber knob are from different serotypes.

Wickham et al. teach:

> In order to make recombinant adenovirus vectors containing targeting sequences, it was first necessary to exchange the knob region of the Ad5 present in a transfer vector with the knob coding region from Ad2, since the HI loop of the Ad2 comprises a unique Spe I restriction site, which allows cloning of particular targeting sequences into this site. Accordingly, the net result of the vector manipulations was to create a fiber chimera in which the DNA encoding the tail and shaft of the fiber are from Ad5, the DNA encoding the knob is from Ad2, and the knob further comprises a nonnative amino acid sequences in the HI loop as depicted in Fig. 1. (column 21, lines 30-41)

In contrast, the present invention teaches it is not necessary to exchange the knob region of the Ad5 with the knob coding region from Ad2. The modified adenovirus in the present invention expresses a modified fiber protein in which the fiber knob and the fiber shaft are from the same serotype (Ad5) (see Example 6). Hence, the modified adenovirus of the present invention is different and distinct from that disclosed in **Wickham**. **Wickham** et al. do not teach or suggest a modified fiber protein expressing fiber knob and fiber shaft from the same serotype as claimed herein.

Wickham et al. teach a second adenoviral modification in which peptide motif is attached to the C-terminal of the fiber protein to create a nonpreexisting loop (Figure 2). **Wickham** et al. teach:

> The invention also provides a means of targeting adenovirus wherein the peptide motifs are presented in a constrained environment at the C-terminus of the fiber protein in the region of the fiber knob. This method entails the generation of loops (i.e. "nonpreexisting loop") by bonding between cysteine residues or through use of other sequences capable of forming loops (e.g. a β-sheet), thereby creating a loop-like structure in the domain of the protein in which the peptide motif is inserted. Generally, according to the invention, the nonnative amino acid sequence being added itself will form a loop-like structure (e.g. through

> disulfide bonding between cysteine residues occurring in vivo). (column 9, lines 12-24)
> The nonpreexisting loop optionally is attached to the C-terminus of the fiber protein or in a fiber knob loop by means of a so-called "spacer" sequence. The spacer sequence may comprise part of the nonnative amino acid sequence proper, or it may be an entirely separate sequence. (column 10, lines 14-18)

In contrast, the present invention does not require attaching peptide motif to the C-terminal of the fiber protein to create a nonpreexisting loop. The present invention also does not require the insertion of a spacer. The present invention simply teaches inserting a peptide into the HI loop of the fiber knob. Hence, the modified adenovirus of the present invention is clearly distinct and less complicated than that disclosed in **Wickham**.

In conclusion, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. **Wickham** et al. do not teach or suggest each and every aspect of the instant invention. The modified adenovirus of the present invention is different and distinct from that in **Wickham** et al. **Wickham** et al. do not teach or suggest making and using of a

modified adenoviral vector as claimed herein. Accordingly, Applicants respectfully request that the rejection of claims 1-4, 6-9, 16, 18-20 and 23 under 35 U.S.C. §102(e) be withdrawn.

The 35 USC §103(a) Rejection

Claims 16 and 22 were rejected under 35 USC §103(a) as being unpatentable over **Wickham** et al. This rejection is respectfully traversed.

As discussed above, the modified adenovirus disclosed herein is different and distinct from that of **Wickham** et al. **Wickham** et al. teach making and using of adenoviral vector modified to express either a chimeric fiber protein (consists of fiber knob and fiber shaft from different serotypes) or a nonpreexisting loop comprising a peptide motif. **Wickham** et al. do not teach or suggest an adenovirus modified by simply inserting a peptide into the HI loop of the fiber knob as disclosed herein.

Claim 16 is drawn to a method of increasing the ability of an adenovirus to transduce primary tumor cells *in vitro* or *ex vivo* by introducing a ligand comprising a tripeptide Arg-Gly-Asp (RGD) into the HI loop domain of the fiber knob of said adenovirus. Since **Wickham** et al. teach away from the present invention and do

not teach or suggest adenoviral modification as described herein, one of ordinary skill in the art would not have the requisite motivation to modify **Wickham** et al. and generate the instant invention. **Wickham** et al. do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 16 and 22 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed February 26, 2003. If any issues remain, the Examiner is requested to telephone the undersigned for immediate resolution.

Respectfully submitted,

Date: July 18, 2003

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